Topics in Primary Care Medicine

Hyperuricemia and Gout

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Hyperuricemia and gout are frequent problems for primary care physicians. In this article the management of asymptomatic hyperuricemia and gouty arthritis are discussed.

Asymptomatic Hyperuricemia

Definition of Hyperuricemia

A serum urate level greater than 8.0 mg per dl in men or 7.0 mg per dl in women is abnormal, because these levels are statistically two standard deviations greater than the population mean. This definition is plausible physiologically because serum becomes saturated with monosodium urate at a concentration around 8 mg per dl. All urate levels in this article refer to the colorimetric method of measuring serum urate that is used in most autoanalyzers. This method is nonspecific; falsely elevated results can be caused by the presence of amino acids, uremia, high doses of vitamin C and levodopa in the test specimen. The uricase method is more specific and gives levels that are lower by 0.4 to 1.0 mg per dl than colorimetric measurements.

True elevations of serum urate can be due to the medical conditions listed in Table 1. Thus, before labeling a patient hyperuricemic, the physician should correct any reversible conditions and repeat the test that yielded an abnormal result, preferably by the uricase method.

Risks of Asymptomatic Hyperuricemia

Our assessment of the risk of asymptomatic hyperuricemia is based on several prospective studies that are flawed by the difficulty in determining how long patients had hyperuricemia before the study began. In most patients with asymptomatic hyperuricemia, symptoms never develop; some have gouty arthritis or a renal stone after many years. Tophi and gouty nephropathy rarely occur before arthritis.

The risk of *gouty arthritis* in men rose with increasing levels of serum urate in subjects of the community-based Framingham study. Gouty arthritis developed in fewer than 2% of patients with a serum urate level lower than 7.0 mg per dl during a follow-up period of 12 years. If the urate level was between 7.0 and 7.9 mg per dl, the risk of arthritis was 17%. If the urate level was between 8.0 and 8.9 mg per dl, the risk was 25%. Ten men had a urate level above 9.0 mg per dl, and in nine of them gouty arthritis developed. Only 179 women had a urate level over 6.0 mg per dl; gouty arthritis developed in 5%.

The incidence of gouty arthritis was lower in another, shorter term study. In only 3 of 69 men with a serum urate concentration greater than 9 mg per dl did gouty arthritis develop during a mean follow-up of four years. Thus, treatment to prevent gouty arthritis may be unnecessary in the short term, even for patients with high urate levels. It is not known if the natural history of hyperuricemia caused by diuretics is different. There are no data on the risk of arthritis at extremely high serum urate levels.

The risk of *renal stones* in patients with asymptomatic hyperuricemia is 3.4 stones per 1,000 patients per year, compared with 1.1 stones annually per 1,000 people without hyperuricemia.

Gouty nephropathy is rare in patients who do not have gouty arthritis, and evidence linking it with asymptomatic hyperuricemia is inconclusive. In one study, azotemia developed in fewer patients with asymptomatic hyperuricemia than in controls. It was projected that even an elevated serum urate level of 12.0 mg per dl sustained over 40 years in an asymp-

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TABLE 1.—*Causes of Elevated Serum Urate Levels*

Drugs
Thiazide-related diuretics
Aspirin (less than 2 grams/day)
Alcohol
Ethambutol
Nicotinic acid
Levodopa
Decreased renal function
Acidosis
Ketosis
Lactic acidosis
Lead intoxication
Moonshine whiskey
Occupational exposure
Excessive purine production
Myeloproliferative disorders
Psoriasis

TABLE 2.—*Clinical Criteria for Primary Gout**

Maximum inflammation within one day
Redness
Involvement of the first metatarsophalangeal joint
Unilateral metatarsophalangeal joint attack
Unilateral tarsal joint attack
Oligoarthritis attack
Asymmetric swelling
Tophus
Hyperuricemia
Complete termination of an attack
More than one attack of arthritis

*Adapted from Wallace SL, Robinson H, Masi AT, et al (*Arthritis Rheum* 1977 Apr; 20:895-900).

tomatic man would increase the serum creatinine level from 1.2 mg per dl to only 2.7 mg per dl. There is no rationale for treating essential hyperuricemia to prevent the development of silent renal disease.

Although hyperuricemia is associated with coronary artery disease, it has not been shown to be an independent risk factor, and there is no evidence that lowering the serum urate level will reduce the incidence of heart disease.

Treatment of Asymptomatic Hyperuricemia

Considering its natural history, most experts recommend no treatment for asymptomatic hyperuricemia. In most patients symptoms do not develop. If gouty arthritis or a renal stone occur they can be treated readily. Little serious harm to a patient is likely if treatment to lower serum urate levels is deferred until symptoms occur.

On the other hand, the disadvantages of drugs that lower serum urate levels are substantial. The annual cost of drugs used is more than $100 per patient and side effects may be significant. The recent experience with ticrynafen, a uricosuric diuretic developed for the "problem" of thiazide-induced hyperuricemia, emphasizes the dangers of using drugs in asymptomatic patients; the drug was withdrawn because of deaths from liver disease. Moreover, compliance with medication taken for an asymptomatic condition may be poor. In decisions about asymptomatic hyperuricemia, physicians will need to explain the risks and benefits to patients, whose preferences ultimately will be decisive.

There are some situations, however, in which asymptomatic patients should be treated. Patients starting cancer chemotherapy should be given allopurinol and fluids to prevent acute uric acid renal tubular blockade. In addition, some experts recommend treating patients who have extremely high serum urate levels—that is, more than 13 mg per dl—or extremely high urine uric acid levels—greater than 1,100 mg per day—because of the projected risks of gouty arthritis or renal stones, even though there is no conclusive evidence to support this practice. If hyperuricemia is due to chronic renal failure, however, the risk of arthritis and stones is so low that prophylaxis is not indicated.

Gouty Arthritis

Clinical Presentation

The classic gouty attack is podagra; about half of first attacks involve the big toe and about 90% of patients with gout eventually have podagra. Inflammation of the first metatarsophalangeal joint, however, is not specific for gout. Diseases that mimic podagra include soft tissue infection, bunions, trauma, calcific periarthritis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, septic arthritis and calcium pyrophosphate deposition disease (pseudogout). Other attacks usually involve a single joint in the legs, with distal joints involved most frequently. Polyarticular attacks may occur, with asymmetric involvement of joints in the legs, sometimes sparing the foot. Attacks may be triggered by alcohol ingestion, trauma, surgical procedures, acidosis, dietary excesses, fasting and drugs that raise or lower the serum urate level.

An acute gouty attack resolves after several days or weeks, even if untreated, though resolution may be much more rapid with appropriate treatment. A total of 62% of patients have a second attack within one year, and 78% have one within two years; 7% do not experience another gouty attack for more than ten years, however.

Evaluation

The arthritis of primary gout may be diagnosed by the clinical criteria listed in Table 2. If six criteria are present, the probability of gouty arthritis (positive predictive value) is 88%. Conversely, if fewer than six criteria are present, the probability that a patient does not have gouty arthritis (negative predictive value) is 97%. Because the patients in this study were solicited from rheumatologists, the sensitivity and specificity of the criteria in other populations may be different.

The serum urate level is normal in 8% of patients with acute gouty arthritis, often because of drugs. Between 9% and 18% of patients with other types of arthritis have elevated serum urate levels.

Joint aspiration is helpful if the diagnosis is uncertain, such as during a first attack, or if septic arthritis is suspected. Fluid specimens should be sent for Gram's stain, culture and examination for crystals. Urate crystals are needlelike and negatively birefringent. Under a red filter, they appear yellow when parallel to the axis of the polarizing filter. In contrast, calcium pyrophosphate crystals seen in cases of pseudogout are blunter and are positively birefringent. False-negative results from tests of joint aspirates occur in 5% of acute gouty attacks.

A therapeutic trial of colchicine is sometimes used as a diagnostic test for gout. Three quarters of patients with acute

gouty arthritis respond to colchicine and those with other forms of arthritis respond occasionally.

Treatment of Acute Gouty Arthritis

Nonsteroidal anti-inflammatory agents usually are effective treatment. Indomethacin is given at dosages of 50 mg every six hours for one or two days, then the dosage is tapered over the next several days. Common side effects are headache, nausea and abdominal discomfort. Dizziness, confusion, peptic ulcer disease, gastrointestinal bleeding and fluid retention also may occur.

Phenylbutazone is also effective, but because it causes more frequent gastrointestinal side effects and, rarely, bone marrow toxicity, many physicians are reluctant to use phenylbutazone for gout. The experience with other nonsteroidal agents is less extensive. Naproxen may be given as a 750-mg loading dose, followed by 250 mg three times a day. There is no conclusive evidence that any one nonsteroidal agent is superior.

Colchicine terminates most acute attacks. It is given by mouth 0.5 mg every hour until relief of pain or side effects occurs. Unfortunately, up to 50% to 80% of patients cannot tolerate colchicine given by mouth because of diarrhea, cramps or vomiting. Many clinicians prefer intravenous administration of colchicine, which avoids gastrointestinal side effects. The dose is 2 mg, which is diluted in 20 ml of saline before injecting into an intravenous line because sclerosis of the vein and extravasation may be painful. A dose of 1 mg may be repeated every 6 to 12 hours if needed. Because of possible bone marrow toxicity, no more than 4 to 5 mg should be given during a single gouty attack. A lower total dose should be given to patients receiving maintenance colchicine or who have liver or renal disease.

Intraarticular injections of steroids are useful in patients who cannot tolerate other drugs. Systemic steroids may be effective, but also may cause rebound attacks.

With many effective drugs available for acute gout, physicians should individualize treatment based on their own experience, the patient's clinical situation and the response of the patient in previous attacks. Both nonsteroidal anti-inflammatory agents and colchicine are more effective if given at the beginning of an attack.

Recurrent attacks of arthritis may be prevented by colchicine at a dosage of 0.5 mg once to three times a day. Recurrent attacks may also be an indication that giving drugs to a certain patient to lower the serum urate level would be helpful. These agents, however, should not be started during an acute attack because they can exacerbate or prolong it.

Tophi

Tophi have become increasingly rare since the widespread use of hypouricemic drugs. Common locations of tophi are the ear, hands, forearm, olecranon bursae and feet.

Renal Stones

Clinical Presentation

Between 10% and 25% of patients with gouty arthritis have renal stones. In 40% of patients, the stones precede arthritis. The risk of renal stones is 1 in 114 patients with gouty arthritis each year. Most stones are composed of uric acid (84%) and are radiolucent; some contain calcium oxalate or phosphate and are radiopaque.

In patients with gout, stones are more common when the concentration of urinary uric acid excretion is higher, occurring in 20% of patients excreting less than 700 mg each 24 hours compared with 35% in patients excreting between 700 and 1,100 mg and 50% in those excreting over 1,100 mg. However, 70% of patients with stones had a normal excretion of less than 700 mg.

The imperfect correlation between serum or urinary uric acid levels and stone formation may be partly explained by urinary pH. Uric acid is ionized and more soluble in alkaline urine; most stone-formers have relatively acidic urine. Because the pK_a of uric acid is 5.75, stones rarely occur if the urine pH is above 6.0. Other risk factors for uric acid stone formation are decreased fluid intake, dehydration, uricosuric drugs and ingestion of purine-rich foods.

Treatment of Stones

Increased fluid intake of more than 2 liters a day and alkalinization of urine to pH 6.0 often prevent further stones. In more severe cases, allopurinol dramatically reduces new stone formation. In addition, allopurinol may dissolve uric acid stones with prolonged administration.

Gouty Nephropathy

Clinical manifestations of gouty nephropathy are decreased concentrating ability, proteinuria or azotemia. Decreased renal function is uncommon, usually mild and often due to concurrent diabetes, hypertension or atherosclerosis. Although clinicians, to prevent azotemia, often administer drugs that lower the serum urate level, there is little evidence such treatment is effective.

Treatment to Lower Serum Urate Levels

When to start treatment to lower serum urate levels is controversial. Some experts recommend starting after one severe attack of arthritis or one renal stone. Many patients, however, prefer not to take daily medication, but instead to treat attacks when they occur. As in any chronic disease, patient understanding and compliance are essential. Taking hypouricemic drugs irregularly may precipitate gouty attacks.

Serum urate levels can be lowered either by a uricosuric agent that increases urinary excretion of uric acid, such as probenecid, or by allopurinol, which decreases production of uric acid. There are no good studies comparing these two approaches. For most patients uricosuric agents are preferred because life-threatening side effects with allopurinol, although rare, are being recognized more frequently.

Allopurinol should be used in patients with renal stones, tophi, renal failure and myeloproliferative diseases and in patients in whom therapy with uricosuric agents has failed and for those who cannot tolerate them. Allopurinol has also been recommended for the 10% to 20% of patients with primary gout who are "overproducers" and therefore overexcreters of uric acid. Overproducers excrete more than 800 mg per day of uric acid on an unrestricted diet or 600 mg per day on a purine-free diet. The rationale for using allopurinol in "overproducers" is that uricosuric agents, by further increasing uric acid excretion, might cause renal stones. The risk of

stones, however, may be overemphasized in patients who do not have previous renal stones, tophi or myeloproliferative diseases. A series reporting a 16% incidence of stones in those on probenecid therapeutic regimens included patients with tophi and previous stones. Physicians in this series did not follow the precaution of starting at low doses and increasing fluid intake. Moreover, in patients without tophi who are given uricosuric agents, the excess uric acid pool is excreted in a few days, after which urinary excretion (and presumably the risk of stones) returns to the original steady-state level.

Administration of uricosuric drugs should be started at low doses and fluid intake increased to prevent renal stones. *Probenecid* therapy is started at 250 mg twice a day, then increased to 500 mg twice a day three to four days later. Subsequently, the daily dose is increased by 500 mg every one to two weeks, to a maximum of 3 grams a day, until the serum urate level is normal. Usually 1 to 2 grams a day are needed. Side effects are gastrointestinal problems in about 8% of patients, skin rashes in about 5% and hypersensitivity reactions. Because probenecid inhibits renal tubular secretion not only of uric acid but also of a number of drugs, the serum concentration of penicillin, cephalosporins, indomethacin and methotrexate is increased.

Treatment with sulfinpyrazone is started at 50 mg twice a day and gradually increased in a similar manner as probenecid therapy. Usually 300 to 400 mg is needed, given in three or four divided doses. Gastrointestinal toxicity is more frequent than with probenecid. Skin rashes and bone marrow suppression may also occur.

In 25% of all patients receiving uricosuric agents normal serum urate levels are not achieved, usually because of azotemia or the concomitant use of low doses of aspirin.

Allopurinol in a single daily dose of 300 mg usually lowers serum urate levels to normal. A few patients require larger doses. Gastrointestinal intolerance has been reported in 0.4% to 16% of patients and skin rashes in 1.8% to 10%. Life-threatening hypersensitivity reactions involving skin, liver and kidney were reported in 2 of 1,835 patients; such reactions are fatal in 26% of cases. Adverse effects are more common in patients with renal failure or those taking thiazides, ampicillin or amoxicillin. Allopurinol may potentiate the therapeutic effect of sodium warfarin, azathioprine and 6-mercaptopurine.

Whenever either a uricosuric agent or allopurinol is given, colchicine, 0.5 mg twice a day, should also be administered to prevent gouty attacks. Therapy with colchicine should be continued until the serum urate concentration has been normal for 6 to 12 months. Limiting intake of alcohol and purine-rich foods and losing weight may reduce symptoms, but rapid weight loss should be avoided because ketosis may precipitate gouty attacks.

A common problem is a patient with recurrent gouty arthritis who takes a diuretic drug. Reasonable approaches are to discontinue giving the diuretic if possible—that is, by using a β-blocker alone for hypertension—to substitute spironolactone or triamterene, which do not increase serum urate, or to add a uricosuric agent.

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